

Tomorrow's asthma therapy – are antiasthmatics in the 90ties anti-inflammatory drugs?

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Asthma affects approximately 5% of population in most industrialized countries and there are indications that its prevalence, severity and mortality is increasing despite intensive drug therapy. Several reasons may explain this situation: a) Asthma displays a complex pathophysiology. It is not a simple bronchoconstriction, but a chronic *inflammatory disease with epithelial exfoliation*; b) Asthma is often underdiagnosed and undertreated. Corresponding to the tradition of this meeting, this review focuses on the inflammation and the possibility of influencing it by drugs in preclinical or clinical development.

Apparently several different cells are involved in the pathogenesis of asthma. These cells produce a variety of mediators which interact in a complex way to produce a number of pathological effects (Fig. 1). Additionally, several neuronal and humoral mechanisms may also contribute to or modify the inflammatory events.

Cells mainly involved in airway constriction and inflammation

Airway smooth muscle hyperplasia is present even in relatively mild asthmatics, possibly as a result of various growth factors released from inflammatory cells, such as platelet- and macrophage-derived growth factors. For many years *mast cells* have been assumed to play a central role in the pathogenesis of asthma. There is no doubt that the role of mast cells has been overestimated. But it can also be stated that their role might have been un-

derestimated. Recent data clearly demonstrate that mast cells are more than simple histamine-releasers. To establish the precise role of mast cells in initiating and maintaining airway inflammation needs further investigation. *Macrophages* are the most prominent resident cells and are present throughout the respiratory tract. There is growing evidence that alveolar macrophages (AM) are involved in almost all steps of airway inflammation, and may have an important role in initiating bronchial asthma and atopy. They can be activated by IgE-dependent mechanisms and release various mediators including cytokines. *Eosinophils* are usually not present in the lung, they will be recruited by chemotactic factors secreted by macrophages, other cells and eosinophils themselves. Eosinophils release a variety of mediators. Although *neutrophil* infiltration is characteristic of some animal models of asthma, the role of neutrophils in human asthma is less certain. Airway *epithelial cells* have attracted interest recently. They may be critical factors in the development of airway inflammation. Epithelial damage may contribute to the inflammation in a number of ways. Besides the loss of epithelial derived relaxing factor (EpDRF) epithelial disruption exposes sensory nerve endings, which can be activated by inflammatory mediators, leading to intensification of inflammation via an axon reflex mechanism. Since *platelets* may be activated by IgE-dependent mechanism and release a host of mediators (e.g. 5- and 12-lipoxygenase products, serotonin, thromboxane), their involvement in asthma appears likely. *T- and B-lympho-*

Figure 1
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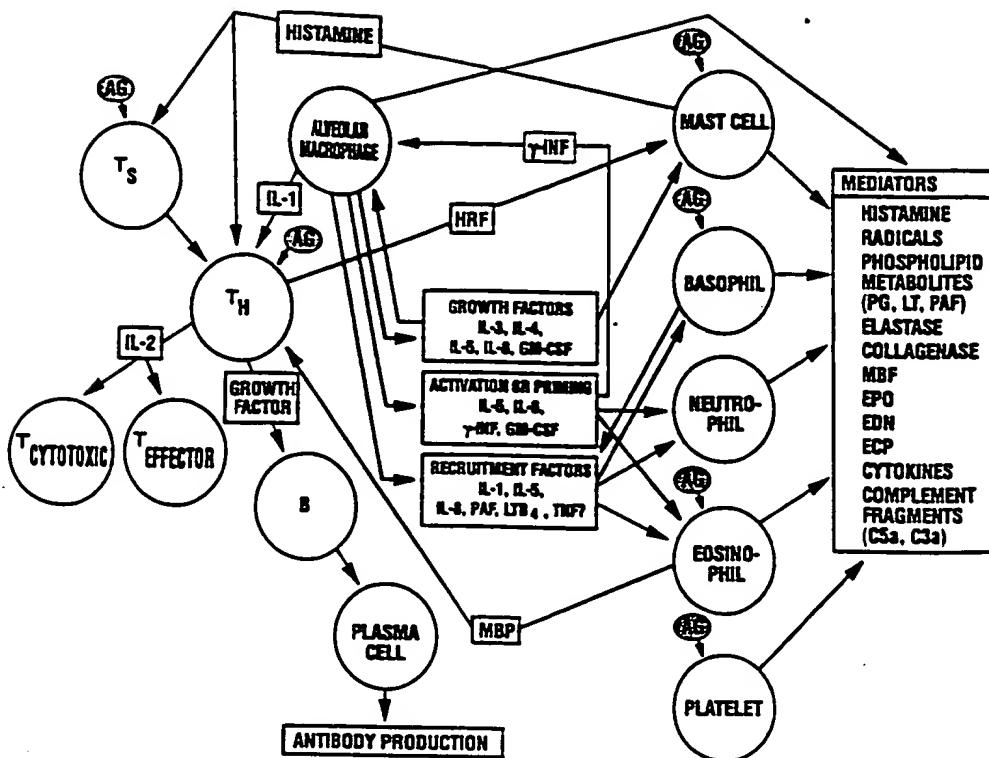


Figure 1

A small part of the complex interactions between cells and mediators participated in the pathogenesis of asthma bronchiale.

early demonstrate multiple histamine-releasing role of mast cells in airway inflammation. *Acrophages* are the and are present. There is growing stages (AM) are in airway inflammation. role in initiating they can be activated and release various. *Eosinophils* are they will be recruited by macrophages. selves. *Eosinophils* although *neutrophil* some animal models in human asth-elial cells have at may be critical fac- way inflammation. due to the inflam- besides the loss of or (EpDRF) epi- nerve endings, mediators. inflammation via an telets may be acti- and release a 12-lipoxygenase), their involve- T- and B-lympho-

cytes appear normally on the pulmonary mucosal surface and in the alveolar spaces. In addition to their role in the regulation of IgE-production, T-lymphocytes and their accessory cells, the alveolar macrophages secrete a number of factors which modulate the activities of other cells in the lung, in particular mast cells, basophils, and eosinophils.

Mediators involved in airway inflammation and their modulation by drugs

The pathomechanism(s) leading to airway smooth muscle contraction are relatively well-known, whereas those initiating the airway inflammation are still far from certain. Several types of inflammatory cells and mediators (not only those mentioned above) are involved in a complex interacting system. Since the exact hierarchy of mediator actions and cell interactions is still unknown, efforts are undertaken by the pharmaceutical industry either to antagonize the effects of mediators or to inhibit their release and/or synthesis. Due to the

extremely rapid development in this field, it cannot be excluded that some compounds or therapeutic ideas mentioned in this review are already out-dated.

Histamine and its novel antagonists (Histamine H₁-antagonists)

Although histamine has been assumed to play a key role in asthma, classical antihistamines have not provided marked clinical benefit in asthma. It has, however, been suggested that there might be an underlying "histamine tone" due to the constant background production and release of histamine secreted by activated mast cells. Novel antihistamines, which do not cross the blood-brain-barrier, have led to a renaissance of this class of drugs. Their exact therapeutic value in asthma management needs further investigation. It can, however, be stated that novel histamine H₁-receptor antagonists, such as terfenadine, astemizole, loratadine have other pharmacological activities in

addition to H_1 -receptor antagonism, which may account for their putative therapeutic usefulness.

Inhibitors of phospholipase A₂

One of the most important source of inflammatory mediators is the *cell membrane phospholipid fraction*, from which phospholipase A₂ releases arachidonic acid and lyso-PAF, two precursor substances of a number of mediators closely associated to airway inflammation.

The key function of PLA₂ mentioned previously makes it interesting as a target for developing new drugs. There are some new compounds which inhibit this enzyme under experimental condition. The recommended indications include almost all diseases accompanied by inflammation. In my opinion, a PLA₂-inhibitor is an interesting candidate for asthma therapy. However, it can be assumed that the inhalation route should be preferred in order to achieve local concentrations without inducing systemic effects.

Arachidonic acid released from cell membrane phospholipids by the action of PLA₂ can be metabolized by the cyclooxygenase pathway to PGs and TXA₂, or by the 5-lipoxygenase pathway to LTs.

Prostaglandins and thromboxanes

Cyclooxygenase (CO)-derived metabolites influence the airway function differently. In general, some PGs such as PGE₂ and PGI₂ dilate the bronchi, others like PGD₂, PGF_{2 α} contract them. However, this schematic classification is apparently not valid for the diseased bronchus. PGE₂ is a potent relaxing PG also in human airways but higher concentrations of this prostanoid which can occur in an inflamed tissue cause constriction. PGs also affect autonomic neurotransmission. Apparently, both presynaptic and postsynaptic actions are operative. The nature of the response seems to be related to the type of PG generated as well as to its concentration. In general, PGE₂ inhibits, and PGF_{2 α} enhances the adrenergic response. Cholinergic responses appear to be enhanced by both PGE₂ and PGF_{2 α} . Based on the variable and in airway inflammation apparently inconsistent effects of PGs it is unlikely that the development of a *stable PG-derivative* for the asthma therapy would be beneficial. The other CO-derived

metabolite, TXA₂, possesses clearcut bronchoconstrictory effects. The idea to enrich the therapeutic arsenal with a *TXA₂ antagonist* or a *TX-synthetase inhibitor*, might be tempting. However, the realisation of this idea would have only scientific value. From therapeutic point of view, there is no evidence that this type of drugs might be superior to bronchodilators available now. The therapeutic significance of *cyclooxygenase inhibitors* is particularly questionable. Potent CO-inhibitors such as flurbiprofen reduce airway hyperresponsiveness to a very limited extent only. The finding that pre-treatment of sensitized human bronchial tissue *in vitro* with indometacin leads to an increased generation of LTC₄ on immunologic challenge with antigen suggests that the inhibition of the CO may lead to an increased generation of LTs as previously described by Brune in peritoneal macrophages and by us using lung tissue obtained from actively sensitized guinea pigs. These results would rather suggest that the administration of CO-inhibitors may aggravate airway inflammation via an intensified imbalance in the arachidonic acid metabolism. However, this shift to the LO-pathway probably is no the only reason of the so-called aspirin-asthma. In subjects with aspirin-induced asthma, a selective and marked increase in airway responsiveness to LTC₄ was demonstrated. After oral desensitization to aspirin, increased airway responsiveness to LTC₄ considerably decreased indicating that the efficacy of desensitization may relate, in part, to a selective down-regulation of LTC₄ receptors in the airways.

Leukotrienes

There is no doubt that LTs are among the key mediators of inflammation. Consequently, compounds with the ability to prevent the synthesis of LTs or to antagonize their effects at the receptor site may be considered as possibly valuable candidates for future management of asthma. Alveolar macrophages (AM) preferentially use the 5-LO pathway. The ratio of 5-LO products to CO products is 4.7:1 for AM but 0.5:1 for peritoneal macrophages. *Inhibitors of 5-lipoxygenase* may have some advantages over pure LT-antagonists. The inhibition of LO results in a full blockade of this metabolic pathway. Several types of this class of drugs are under development. In principle, the fate of each new drug depends on its side-effect

inducing potent inhibitors of 5-LO up to now that vital enzyme sys side-effects. The able, such as pir specific and of lc have significant Recent work has siveness to the su matic subjects m and LTE₄. The r of the bronchoco tinct from that f asthmatics. This heterogeneity in as the possibility exi LTD₄ may not ! LTE₄ is the mos and appears to b the BAL fluid of specific LTC₄ an effective in the tr has a unique role then one should LTE₄ antagonists the treatment of b be very likely tha ful. If all three LT of asthma, it wil which block each taking both for t for the patients! N tion that the over LT-antagonists at Thoracic Society was negative. The drugs to affect rel lead to the conclu going to play a ma however, notewor lieved that the "t nists are even be antagonists conta ety and are based tion, LY-171.883 ever, it was rec studies not becau rather chronic to rat. The *second g turally related to*

clearcut bronchoconstrictor or a TX-synthetase. However, the realisability scientific value. Now, there is no evidence that the therapeutic inhibitors is particularly superior to the TX-synthetase. The therapeutic inhibitors such as TX-synthetase inhibitors are finding that pre-bronchial tissue in an increased generic challenge with the CO may of LTs as previous results would rather than of CO-inhibitors action via an intrinsic acid metabolism. Bronchial pathway probably is led aspirin-asthma. In asthma, a selective TX-synthetase inhibitors to oral desensitization indicating that the relate, in part, to a TX₄ receptors in the

inducing potential. It is particularly valid for the inhibitors of 5-LO. We have learnt from experience up to now that LO-inhibitors often affect other vital enzyme systems resulting in life-threatening side-effects. The 5-LO-inhibitors currently available, such as piroprost and nafazatrom, are non-specific and of low potency and do not appear to have significant clinical effects in asthma.

Recent work has shown that the airways responsiveness to the sulfidopeptide leukotrienes in asthmatic subjects may be different for LTC₄, LTD₄ and LTE₄. The results suggest that the mechanism of the bronchoconstriction induced by LTE₄ is distinct from that produced by LTC₄ and LTD₄ in asthmatics. This may reflect LT receptor subtype heterogeneity in asthmatic airways. If this is correct, the possibility exists that antagonists for LTC₄ and LTD₄ may not be effective against LTE₄. Since LTE₄ is the most stable metabolite of these LTs, and appears to be the predominant one found in the BAL fluid of patients with bronchial asthma, specific LTC₄ and LTD₄ antagonists may not be effective in the treatment of this disease. If LTE₄ has a unique role in the pathogenesis of asthma, then one should consider the development of LTE₄ antagonists or LTC₄ synthetase inhibitors for the treatment of bronchial asthma. It can however, be very likely that the latter approach is more useful. If all three LTs are involved in the pathogenesis of asthma, it will be important to develop drugs which block each receptor type. A difficult undertaking both for the pharmaceutical industry and for the patients! Moreover, it is of interest to mention that the overall impression with regard to the LT-antagonists at the conference of the American Thoracic Society (1989, Cincinnati, Ohio, USA) was negative. The consistent failure of this class of drugs to affect relevant models of asthma may now lead to the conclusion that LT-antagonists are not going to play a major part in asthma therapy. It is, however, noteworthy to mention that it is still believed that the "third generation" LTD₄ antagonists are even better. The first generation LTD₄ antagonists contain a hydroxyacetophenone moiety and are based on FPL-55.712. Of this generation, LY-171,883 was the most advanced. However, it was recently withdrawn from clinical studies not because of lack of efficacy in man but rather chronic toxicological manifestations in the rat. The second generation antagonists are structurally related to peptidoleukotrienes. For example,

SKF-104,353 is the culmination of a series of structural modifications. This agent is under development only as an aerosol. Since members of the third generation LTD₄ antagonists bear little resemblance to LTD₄, the only common structural feature is an acidic moiety, they have been classified as "third generation" antagonists. Preclinical results are promising. Clinical data are not yet available.

Interestingly, relatively little interest has been paid to LTB₄, at least, until now. Apart from its direct chemotactic effect, LTB₄ may induce the secretion of other chemotactic factors, e.g. AM secrete a neutrophil chemotactic factor upon LTB₄ stimulation. Moreover, LTB₄ increases the synthesis and release of interleukin (IL)-1. It can, however, be believed that the role of LTB₄ in asthma pathogenesis is of minor significance, probably, due to the lack of its influence on the bronchial smooth muscle. Specific LTB₄ antagonists are not in drug development, at least, to my knowledge. NAT 04-159 from Nattermann selectively inhibits LTB₄-formation. However, it did not reach the clinical development stage.

Platelet-activating factor and its antagonists

Platelet-activating factor (PAF), another lipid mediator, mimics many, but not all, of the pathological features of asthma and causes as the only mediator a sustained increase in bronchial activity in humans. These observations have led to an intensive research for PAF antagonists. A mixture of ginkgolides A, B and C (BN52063) inhibits PAF-induced skin wheel and clear responses and platelet aggregation in man. If this can be extended to the airways in asthma then drugs with this form of activity might hold great promise. Several antagonists other than ginkgolides are also under clinical investigation. The first clinical results are disappointing. It is very likely that the therapeutic significance of the PAF antagonists has been overestimated. A number of mediators are involved in the complex pathogenesis of asthma. And PAF is only one of them! It is likely that in no instance a single mediator accounts for asthma in general. But in any circumstances, the role of PAF may be very important!

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Sensory neuropeptides

It can be assumed that viral infections or environmental factors affect the protective epithelial cells in the respiratory tract which either result in decay of these cells or in direct stimulation of unmyelinated c-fibres. Moreover, it is also possible that resident lung cells secrete monokines or LO-derived metabolites which are chemoattractant for eosinophils which, once activated, release basic proteins toxic for the respiratory epithelium (neurogenic inflammation). Damage to airway epithelium exposes c-fibre afferent nerves which can then be triggered by inflammatory mediators such as bradykinin, resulting in the release of *sensory neuropeptides* such as substance P (SP), neurokinin A (NKA), calcitonin gene-related protein (CGRP), from collaterals of these nerves (axon reflex). These neuropeptides induce bronchoconstriction, microvascular leakage and increased mucus secretion. SP also degranulates mast cells and possesses chemotactic activity. Substance P neurones were found to be increased in both number and length in asthmatic airways. These observations provide further support for the proposal that autonomic imbalance may be important in the pathophysiology of asthma. However, it is important to bear in mind that these changes may be secondary to some process such as the secretion of nerve growth factors from inflammatory cells. Antagonists of sensory neuropeptides currently available are not very

potent or specific. It is likely that inhibition of the release of these peptides is a more relevant therapeutic approach.

Clonidine, an α_2 -adrenoceptor agonist, inhibits sensory neuropeptide release from guinea-pig airways. Whether α_2 -adrenoceptor agonists would succeed into the therapy of bronchial asthma is, however, more than questionable. With regard to the receptor-G-protein interaction, it is known that stimulation of α -adrenergic receptors results in an inhibition of adenylate cyclase. It is opposite to the effect induced by activation of β_2 -adrenoceptors operating on the same adenylate cyclase system (Fig. 2). This is the reason why α_2 -adrenoceptor antagonists but not agonists as bronchodilators are now developed for asthma therapy. Opioid μ -receptor agonists are also able to inhibit this axon reflex. Such a compound seems to be more promising when it is free of histamine releasing effect of morphine.

Bradykinin-antagonists may belong to the future antiasthma drugs. Previous reports that bradykinin can evoke late-phase reactions in the skin have led to study the effects of a bradykinin antagonist (NPC-567) in a sheep model of asthma. This compound had no effect on the immediate asthmatic response but abolished the increase non-specific responsiveness and also attenuated the cellular changes in BAL.

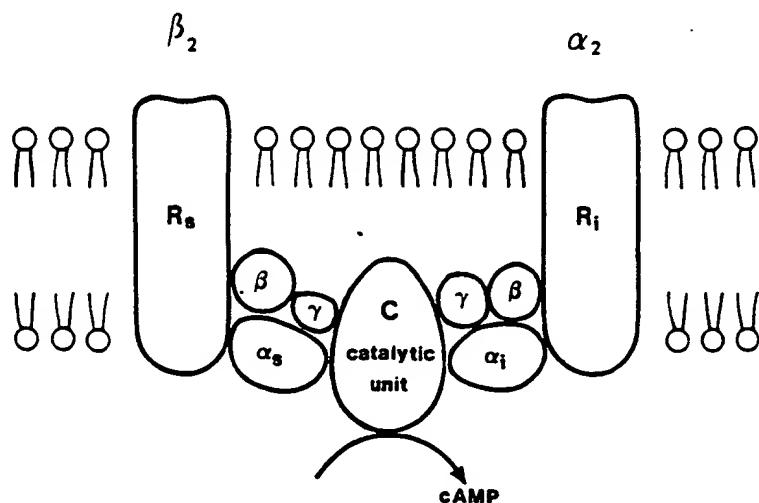


Figure 2
Possible interaction between α_2 - and β_2 -adrenoceptor agonists: stimulation of α_2 -adrenoceptor results in activation of inhibitory G protein leading to diminished production of cAMP.

Bronchodilatory α_2 -agonists have been indentified in the *small peptide* (VIP) smooth muscle airways. Enzymes degrade VIP of effect of a brachial cholinergic nerve activated bronchoconstriction. VIP increases the release of histamine tribute to its brachial and other neurotrophins (PHM). (PHM) have only a role in the inflammation, even the bronchial bronchi and bronchitis.

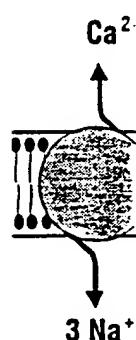


Figure 3
Calcium movement (see text) (ROC = receptor)

at inhibition of the more relevant therapy.

agonist, inhibits from guinea-pig airways. α_2 -agonists would be useful in bronchial asthma. With regard to this, it is known that α_2 -receptors results in bronchoconstriction. It is opposite to the action of β_2 -adreno-adenylate cyclase on why α_2 -adreno-agonists as bronchodilators in asthma therapy. It is also able to inhibit the bronchoconstriction caused by histamine release.

long to the future are reports that these reactions in the cells of a bradykinin model of asthma. On the immediate and the increase non-attenuated the cel-

Bronchodilatory neuropeptides

Many other different neuropeptides have now been identified in the airways. *Vasoactive intestinal peptide* (VIP) is a potent relaxant of airway smooth muscle and is a cotransmitter in cholinergic nerves. Enzymes released from inflammatory cells degrade VIP very rapidly in asthma. The lack of effect of a bronchodilatory transmitter at the cholinergic nerve endings may lead to an exaggerated bronchoconstrictor response to vagal stimulation. VIP increases blood flow and thus, the removal of histamine, an effect which may also contribute to its bronchodilator activity. Since VIP and other neuropeptides such as peptide histidine isoleucine (PHI), peptide histidine methionine (PHM) have only muscle-relaxant activities, their role in the inflammation may be excluded. However, even the bronchodilatory activity of VIP is limited, since VIP-receptors are not present in small bronchi and bronchioles.

A pivotal role of calcium in respiratory inflammation?

In the broadest sense, all of the pathological events in asthmatic airways are Ca^{2+} -dependent phenomena (Fig. 3). With regard to the pivotal role of Ca^{2+} -ions in inflammation, one can expect that compounds acting on cellular Ca^{2+} turnover may be promising candidates for future asthma therapy. Drugs which inhibit Ca^{2+} release from intracellular stores may have beneficial effects both in airway smooth muscle and in inflammatory cells. A prototype of this class of drug is TMB-8. A further therapeutic approach is to inhibit the activation of the Ca^{2+} -binding protein calmodulin. Calmodulin antagonists are available, but their clinical value is questionable, since calmodulin occurs ubiquitously and controls the activity of many enzyme systems in the whole organism. Breakdown of phosphoinositides (PI) in the cell membrane by stimulation of surface receptors initiates

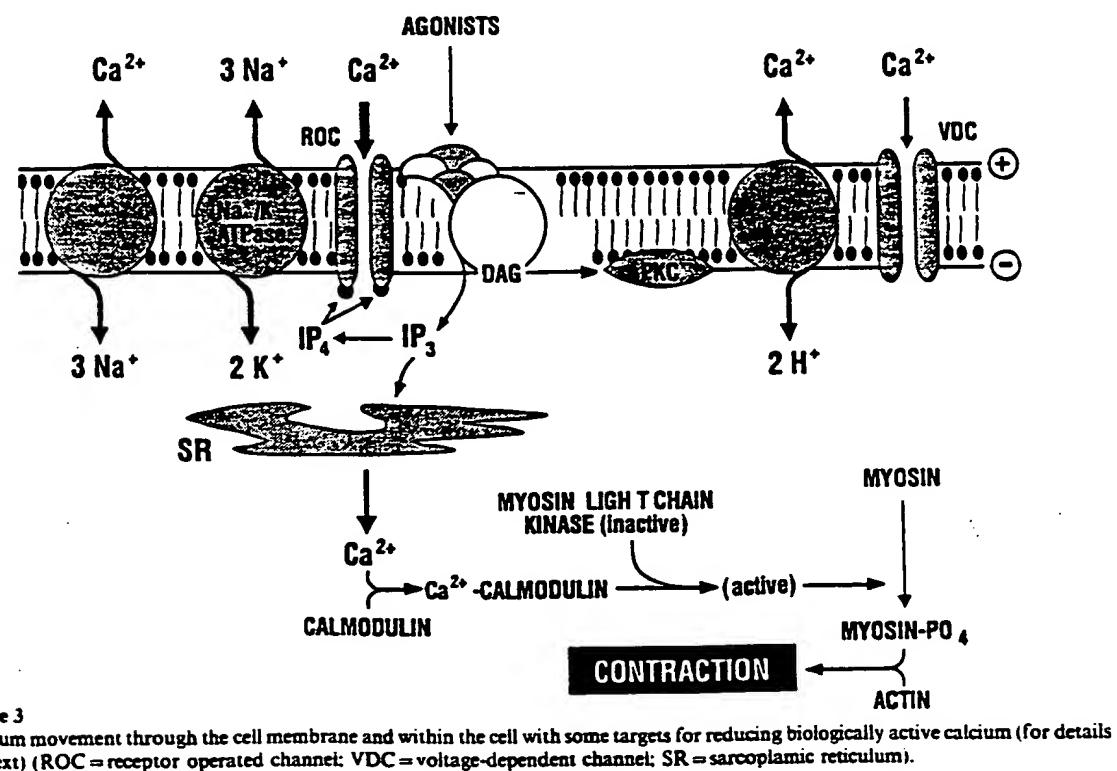


Figure 3

Calcium movement through the cell membrane and within the cell with some targets for reducing biologically active calcium (for details see text) (ROC = receptor-operated channel; VDC = voltage-dependent channel; SR = sarcoplasmic reticulum).

the release of Ca^{2+} from the sarcoplasmic reticulum and regulates Ca^{2+} entry via receptor-operated channels. Drugs which inhibit the activation of PI system (PLC-inhibitors?) or antagonize IP_3 and/or IP_4 at their target site may be useful and are now being developed. Drugs with the ability only to inhibit Ca^{2+} influx via blocking voltage dependent channels have extremely low or no chance in the asthma therapy due to relatively high intracellular Ca^{2+} concentration of the bronchial muscle.

Will corticosteroids remain the only choice in the Nineties?

There is no doubt that *corticosteroids* are the most effective drugs currently available for the long-term management of asthma. Since they suppress virtually every stage of the inflammatory response in asthmatic airways, steroids probably be introduced much earlier in the therapy. The precise mode of their action is still unknown. Steroids supposedly stimulate the production of lipocortin, which, in turn, inhibits PLA_2 . There are, however, some doubts: whether lipocortin is really involved in mediating steroid effects and whether all effects of steroids are mediated via PLA_2 inhibition. Future steroids should have an even higher potency, they should be metabolized locally, so that the inhaled dose can be increased without any systemic which currently limit dose.

Is the classical immunotherapy at a cross-roads?

The availability of modern technology using molecular biology tools as well as the better understanding of the mechanisms of *immunotherapy* leads to the expectation of improvements in immunotherapy. Concerning the classical immunotherapy, the hyposensitization, it was put on trial at the National Heart & Lung Institute, Brompton Hospital, London in April 1988. The official verdict was a tie - 50% for immunotherapy and 50% against immunotherapy. According to the opinion of leading personalities for immunotherapy, hyposensitization is a useful, safe and effective treatment in allergic disease if it is performed according to the guide-lines of the European Academy of Allergology and Clinical Immunology. Opponents of immunotherapy, of course, do not believe that it would be safe and effective. Physicians usually swear an oath of Hippocrates containing the fa-

mous sentence: *Nil nocere!* This is the most important point among the arguments against hyposensitization: deaths from hyposensitization injections are appreciable, whereas deaths from allergic rhinitis are zero! Immunotherapy remains mysterious, nobody knows how it works. Pharmacotherapies currently available are clearly effective and safe (and incomparably cheaper). "Summa summarum", the pharmacologist clearly votes against hyposensitization. However, he still believes that immunotherapy in a broader sense belongs to the interesting fields of future allergy/asthma therapy. Several possibilities are now envisaged such as the modulation of IgE synthesis by suppressor factors and antilymphocytic drugs, blockade of the allergic reaction at the effector cell level by inhibition of IgE receptor expression or by compounds structurally related to the IgE receptor.

Novel trends in the immunotherapy

Among the future possibilities, *antilymphocytic drugs* are already available. Cyclosporin A, which inhibits the function of T lymphocytes, and the expression of IL-2 receptors, has proven to be effective in steroid-resistant asthma. A new generation of related drugs which lack nephrotoxicity is under development. Understandably, the interest in *cytokines* is high and steadily increasing. For long time, IL-1, TNF, GM-CSF and some other appeared to be the most important lymphokines in the airway inflammation. Nowadays, the interest is focused on the newly discovered IL-8. It is produced by a number of different cell types and is chemotactic for neutrophils. There is now convincing evidence that IL-8 is produced by monocytes and alveolar macrophages in response to stimulation with bacterial LPS, TNF or IL-1 β . It seems likely that the variable chemotactic activity reported in TNF and IL-1 preparations was actually due to induction of IL-8. Due to the lack of specific lymphokine-antagonists, their therapeutic usefulness cannot be estimated today.

Is the near future the domaine of multifaceted drugs?

The pathogenesis of asthma is still elusive although recently several advances have been made in our understanding of this disease. We have to keep in mind that *no mediator alone can account for the different aspects of a disease as complex as asthma*

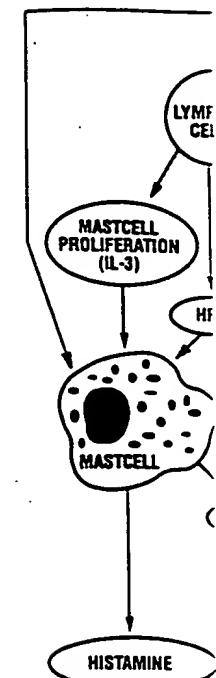


Figure 4
Complexity of cellular bronchial asthma. which, in turn, enhances Activation of lymphocytic mast cell proliferating factor increases ECF-A (eosinophil ciliated body) production by A.M.

as stated by Sir. ple clearly dem involved in bronchial asthma drugs (Fig. 4): alveolar macrophages mutual influence lymphokines lymphokine (IL-1, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, IL-18, IL-20, IL-22, IL-23, IL-25, IL-27, IL-30, IL-31, IL-32, IL-33, IL-34, IL-35, IL-36, IL-37, IL-38, IL-39, IL-40, IL-41, IL-42, IL-43, IL-44, IL-45, IL-46, IL-47, IL-48, IL-49, IL-50, IL-51, IL-52, IL-53, IL-54, IL-55, IL-56, IL-57, IL-58, IL-59, IL-60, IL-61, IL-62, IL-63, IL-64, IL-65, IL-66, IL-67, IL-68, IL-69, IL-70, IL-71, IL-72, IL-73, IL-74, IL-75, IL-76, IL-77, IL-78, IL-79, IL-80, IL-81, IL-82, IL-83, IL-84, IL-85, IL-86, IL-87, IL-88, IL-89, IL-90, IL-91, IL-92, IL-93, IL-94, IL-95, IL-96, IL-97, IL-98, IL-99, IL-100, IL-101, IL-102, IL-103, IL-104, IL-105, IL-106, IL-107, IL-108, IL-109, IL-110, IL-111, IL-112, IL-113, IL-114, IL-115, IL-116, IL-117, IL-118, IL-119, IL-120, IL-121, IL-122, IL-123, IL-124, IL-125, IL-126, IL-127, IL-128, IL-129, IL-130, IL-131, IL-132, IL-133, 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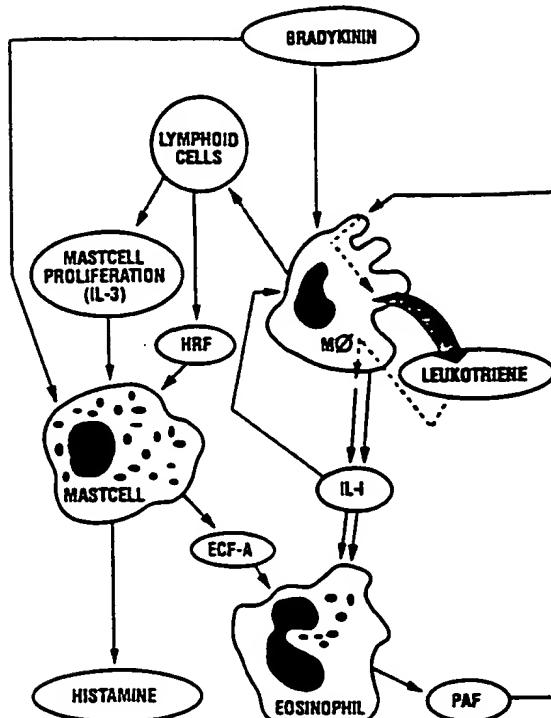


Figure 4

Complexity of cellular and humoral factors in involvement of bronchial asthma. Alveolar macrophages release leukotrienes which, in turn, enhance IL-1 production and release from AM. Activation of lymphoid cells results in IL-3 production leading to mast cell proliferation. Lymphoid cells-derived histamine releasing factor increases histamine release. Eosinophils recruited by ECF-A (eosinophil chemotactic factor of anaphylaxis) and activated by IL-1 release PAF which, in turn, enhances leukotriene production by AM.

as stated by Sir James Black. The following example clearly demonstrates the complexity of events involved in bronchial asthma and its influence by drugs (Fig. 4): Besides the interaction between alveolar macrophages and T cells, there is a close mutual influence between leukotrienes and lymphokines also existent. LTs enhance lymphokine (IL-1) secretion from AM, and vice versa. IL-1 stimulates LT synthesis and release. IL-1 activates lymphocytes to release IL-2 which then induces activation and replication of several subsets of precursor lymphocytes. Both IL-2 and LTs enhance the production of interferon-gamma (γ -INF), which, in turn, produces a number of immunomodulatory effects including expression

of Ia on macrophage cell membrane, activation of oxidative metabolism and also modulates the release of eicosanoids. This cascade of cytokines, in collaboration with arachidonate metabolites, regulates immunity and sets the stage for many of the events underlying inflammation. In this scheme it appears improbable that selective inhibition of one component (e.g. IL-1 antagonist) or one enzyme (e.g. 5-LO inhibitor) would do more than create an imbalance in this closely integrated network of mediators. Drugs with a broad spectrum of antagonistic activity may have a greater chance to stop the cascade of different mediators which often intensify reciprocally each other.

Multifaceted drug of the first generation

Based on the broad pharmacological activities of azelastine, it might be the first representant of drugs with the ability to act at different sites of asthma pathogenesis (Szelenyi, 1989; Szelenyi et al. 1990). To demonstrate its many-sided pharmacological activities, two interesting properties found recently are presented here. Azelastine effectively inhibits superoxide generation both in human polymorphonuclear leukocytes (PMNL) and in guinea pig alveolar macrophages (Fig. 5). There is evidence that azelastine probably interacts with the enzyme protein kinase C (PKC) which directly activates NADPH⁺ oxidase resulting in superoxide radical generation (Schmidt et al. 1990). Dr. Paegelow showed at this meeting that azelastine is able to reduce the IL-1-concentration in the pleural fluid of mice during a nonspecific inflammation. Recently, we have found that azelastine, similarly to dexamethasone, inhibits the release and/or synthesis of IL-1 induced by LPS from human PMNL (Fig. 6). These effects of azelastine cannot simply be explained by its histamine H₁-antagonistic activity. It has been demonstrated that azelastine considerably inhibits LT release from the lung tissue after allergen challenge. On the basis of the well-known mutual interaction between LTs and IL-1, it is likely that inhibition of LT synthesis and/or release by azelastine leads to a diminished production/secretion of IL-1. The overall pharmacological profile of azelastine may suggest that this type of compounds with a strong bronchodilatory effect will be needed in the future asthma therapy.

Outlook

To prevent or would be reason tion. Besides cor able today whic This handicap in overcome. At prtic potential in animal and hum will enrich the d within the next fe asthma therapy inflammatory mation, respectiv that we need druous pharmacolog Consequently, m to antagonize se are needed. And an additional ant activity, this drug 90ties!

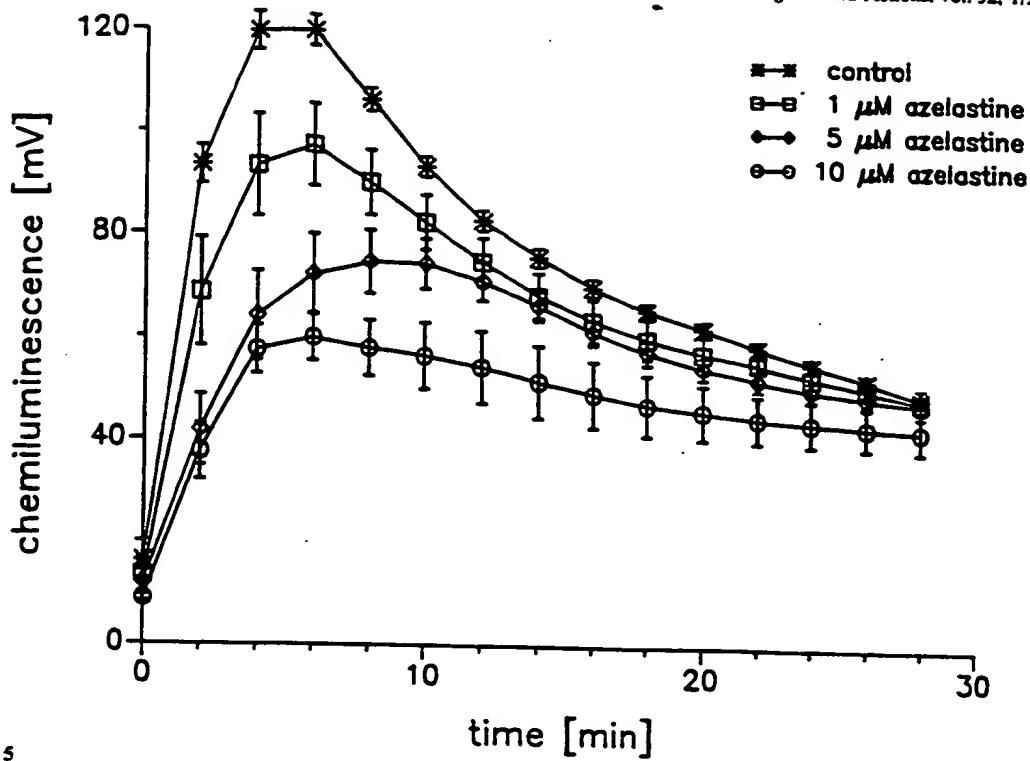


Figure 5
Azelastine inhibits superoxide generation in guinea pig alveolar macrophages.

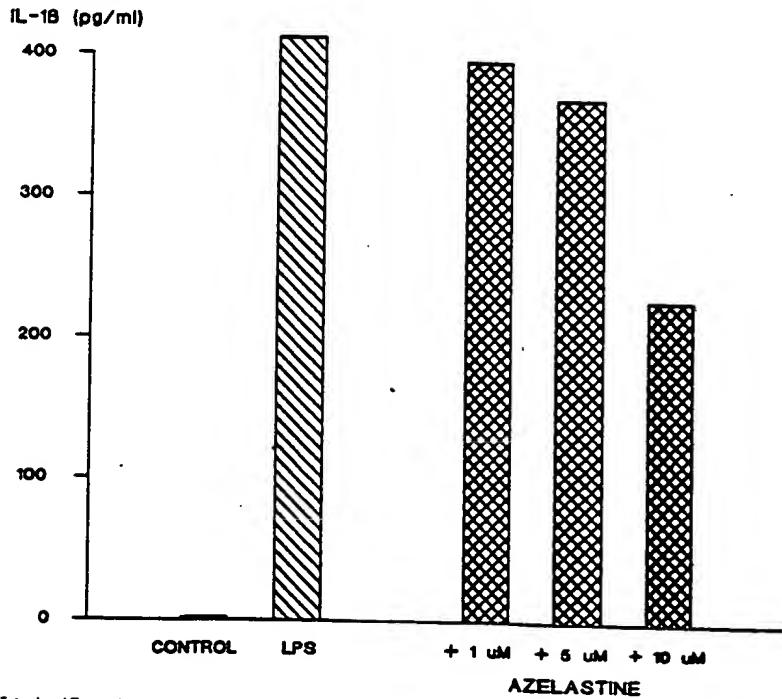


Figure 6
Azelastine (10 μmol/L) significantly reduces IL-1 release from human leukocytes stimulated by lipopolysaccharide (LPS).

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azelastine

azelastine

azelastine

Outlook

To prevent tomorrow's airway obstruction it would be reasonable to inhibit today's inflammation. Besides corticosteroids there is no drug available today which would meet this requirement. This handicap in today's asthma therapy should be overcome. At present, many drugs with therapeutic potential in asthma are being investigated in animal and human studies. One or probably more will enrich the daily therapy of asthmatic patients within the next few years. Further developments in asthma therapy should be directed towards the inflammatory mechanisms. Asthma and inflammation, respectively, are much more complex so that we need drugs with a broad spectrum of various pharmacological activities.

Consequently, multifaceted drugs with the ability to antagonize several mediators of inflammation are needed. And when such a compound possesses an additional and relatively high bronchodilatory activity, this drug would be the "cimetidine" of the 90ties!

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